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Visual Circuits Get the VIP Treatment

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Behavioral state, specifically locomotion, has been shown to enhance sensory responses in primary visual cortex. In this issue of *Cell*, Fu et al. reveal the circuit elements that mediate this plasticity and suggest that these circuits may serve a general modulatory function across primary sensory areas.

Classically, primary sensory cortex has been thought to faithfully transmit information about the physical world that the organism can use to navigate and react to its environment—any variation was thought to arise in later (i.e., higher cortical) stages of processing. Thus, an initial report from Niell and Stryker that locomotion caused a two- to three-fold increase in the sensory response of neurons in the mouse primary visual cortex (V1) came as a major surprise (Niell and Stryker, 2010). Since then, a variety of behavioral states including sensorimotor mismatch and fear association have been shown to alter the sensory-evoked responses of primary cortical neurons (Keller et al., 2012; Letzkus et al., 2011). Such findings have helped legitimize the mouse as a model for studying cortical function: not only are cortical neurons in the mouse well-tuned to specific sensory stimuli, but they are also modulated in ways that are reminiscent of classic attentional effects in nonhuman primates. Moreover, with its genetic and experimental tractability, the mouse promises to reveal the cellular and circuit mechanisms that are necessary for flexibility and learning in sensory processing. In this issue of *Cell*, Fu et al. (2014) take advantage of these powerful tools to identify the neural circuit that integrates locomotor activity with visually-evoked responses (Figure 1).

The initial report from Niell and Stryker, and subsequent electrophysiology experiments in head-fixed mice running on a trackball, have provided important clues to the potential underlying mechanisms. First, no modulation was observed in sensory thalamic nuclei, suggesting that any changes must occur locally within V1 (Niell and Stryker, 2010). Second, the increase in responsivity was not accompanied by a change in tuning width, consistent with a mechanism involving a multiplicative effect on the neuronal response (i.e., a change in cortical gain; Niell and Stryker, 2010; Polack et al., 2013). Gain changes can be caused by alterations in the balance of excitation and inhibition, and indeed, while both excitatory and inhibitory conductances are increased during locomotion, changes in excitation surpass inhibition (Bennett et al., 2013). Finally, the transitions between brain states are as rapid as the behavioral transitions and depend on the running speed (Niell and Stryker, 2010; Saleem et al., 2013), suggesting that the signaling mechanism must be both fast and closely tied to the motor system. Yet, the local circuit mechanisms that mediate this increase in visually-evoked responses, as well as the neuromodulatory systems that are engaged during locomotion, remain undefined.

In this issue, Fu et al. conduct an elegant study designed to reveal the specific class of neurons in V1 that are directly modulated by locomotion (Fu et al., 2014). Here, they focus on a class of interneuron targeting interneurons that express vasoactive intestinal protein (VIP) and have been previously shown to mediate changes in the balance of excitation and inhibition (Pfeffer et al., 2013). By using two-photon calcium fluorescence imaging to monitor the activity of layer 2/3 neurons in a mouse with genetically labeled VIP neurons, the authors find that the majority of unlabeled neurons (putative pyramidal cells) showed no changes in their spontaneous activity. However, there is a striking correlation between the calcium signals in VIP neurons and bouts of running. To demonstrate that this relationship is not merely a correlation, Fu et al. show that direct activation of VIP cells is sufficient to increase visual responses of neighboring neurons, mimicking the effects of locomotion. Moreover, ablation of VIP neurons blocks the effects of locomotion, strongly suggesting that the activity of VIP neurons can account for most of the modulation of V1 in response to locomotion.

The specific recruitment of VIP neurons by locomotion sets the stage for direct modulation of V1 through a disinhibitory mechanism. Since VIP neurons in V1 are known to provide a major source of inhibition to somatostatin (SST) expressing interneurons (Pfeffer et al., 2013) (Figure 1), Fu et al. next test the effect of locomotion on these neurons. Accordingly, they find that while parvalbumin (PV) expressing neurons could be both enhanced and suppressed, SST neurons were uniformly suppressed by locomotion. Suppression of SST neurons results in a decrease in dendritic inhibition onto pyramidal cells, which in turn generates an increase in V1 responsivity (Figure 1). Thus, manipulating VIP cell activity provides an efficient mechanism for rapidly changing gain in the visual cortex. Indeed, this disinhibitory circuit has also been described in other primary sensory areas, and may be a general means by which behavioral state can modulate sensory processing (Lee et al., 2013; Letzkus et al., 2011; Pi et al., 2013). Moreover, given that Fu et al. find similar modulation of VIP neurons in both auditory and somatosensory cortices, the disinhibitory effects

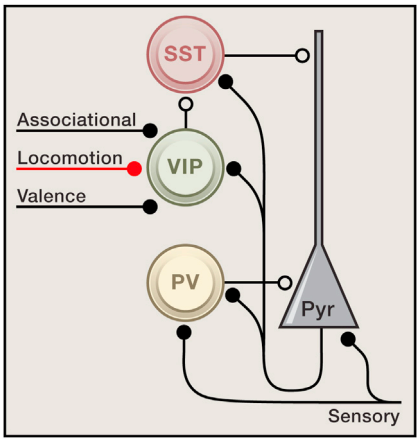

Figure 1. Circuit Model for the Enhancement of Sensory Responses by Locomotion
Sensory signals enter the cortex and excite pyramidal cells which in turn excite PV, SST, and VIP expressing interneurons, generating strong recurrent inhibition. Locomotion signals are conveyed to the cortex via cholinergic inputs that excite VIP expressing interneurons and in turn inhibit SST interneurons, thereby decreasing feedback inhibition onto pyramidal cells (PYR). This type of disinhibitory circuit may also be driven by other behavioral states that are salient in primary sensory cortices. Closed circles: excitatory synapses; open circles: inhibitory synapses.

of locomotion may also be a general feature of cortical processing.

But what is the input that drives the VIP neurons' response to locomotion? To reveal the source of this motor-dependent modulation, Fu et al. use a viral approach to retrogradely label the population of neurons that provide synaptic input to VIP neurons. This approach shows a strong input from cholinergic neurons in the basal forebrain, but only a sparse glutamatergic input from secondary motor cortex. Consistent with the anatomy, glutamatergic antagonists have no effect on the locomotion dependent modulation of VIP neurons, while nicotinic antagonists significantly reduce the correlation of VIP cells with running. These technically challenging experiments strongly suggest the involvement of the basal forebrain in driving the effects of locomotion. However, the anatomy and pharmacology also leave room for contributions from other neuromodulatory systems (see Polack et al., 2013), and additional manipulations of this pathway are needed to determine whether basal forebrain activity is either necessary or sufficient. Moreover, wheel-running is a complicated behavior that could potentially engage multiple neuromodulatory systems through motor, arousal, stress, and reward pathways depending on the specific behavioral state of the animal.

Future experiments to understand the specificity of this pathway will highlight the impact of this study. For instance, it will be important to determine whether different information carried by cholinergic pathways (e.g., arousal, locomotion, punishment) is carried by the same afferent fibers (Letzkus et al., 2011; Fu et al., 2014; Pi et al., 2013), and activates the same population of VIP neurons in sensory cortex (Figure 1). Experiments testing the coincident engagement of these different behavioral states will reveal how such disparate signals can be integrated. Finally, it will be important to understand how neuromodulatory inputs are in turn gated by sensory inputs: Fu et al. make the interesting observation that VIP cells actually become less correlated with locomotion during visual stimulation and that this effect is dependent on glutamatergic transmission. Since past experiments have shown that locomotion can enhance visual performance (Bennett et al., 2013), understanding the interaction between sensory and neuromodulatory pathways will be necessary to help us make hypotheses about what the plasticity generated by these circuits ultimately achieves.

REFERENCES

Bennett, C., Arroyo, S., and Hestrin, S. (2013). Neuron *80*, 350–357.

Fu, Y., Tucciarone, J.M., Espinosa, J.S., Sheng, N., Darcy, D.P., Nicoll, R.A., Huang, Z.J., and Stryker, M.P. (2014). Cell *156*, this issue, 1139–1152.

Keller, G.B., Bonhoeffer, T., and Hübener, M. (2012). Neuron *74*, 809–815.

Lee, S., Kruglikov, I., Huang, Z.J., Fishell, G., and Rudy, B. (2013). Nat. Neurosci. *16*, 1662–1670.

Letzkus, J.J., Wolff, S.B., Meyer, E.M., Tovote, P., Courtin, J., Herry, C., and Lüthi, A. (2011). Nature *480*, 331–335.

Niell, C.M., and Stryker, M.P. (2010). Neuron *65*, 472–479.

Pfeffer, C.K., Xue, M., He, M., Huang, Z.J., and Scanziani, M. (2013). Nat. Neurosci. *16*, 1068–1076.

Pi, H.J., Hangya, B., Kvitsiani, D., Sanders, J.I., Huang, Z.J., and Kepecs, A. (2013). Nature *503*, 521–524.

Polack, P.O., Friedman, J., and Golshani, P. (2013). Nat. Neurosci. *16*, 1331–1339.

Saleem, A.B., Ayaz, A., Jeffery, K.J., Harris, K.D., and Carandini, M. (2013). Nat. Neurosci. *16*, 1864–1869.